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The *BRCA1/2* Parent-of-Origin Effect on Breast Cancer Risk—Response

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With great interest, we read the letter to the editor from Evans and colleagues (1) on the parent-of-origin effect on breast cancer risk in *BRCA1/2* mutation carriers, which addressed our recent findings on this issue (2). In our Dutch national cohort of *BRCA1/2* mutation carriers, no parent-of-origin effect was observed after careful consideration of ascertainment bias. Evans and colleagues confirm these findings in a larger, prospectively collected, cohort of *BRCA1/2* mutation carriers from northwest England, and they corroborate the importance of correcting for ascertainment bias. This independent validation of our results supports our conclusion that there is no parent-of-origin effect on the breast cancer risk of *BRCA1/2* mutation carriers and that this apparent phenomenon is due to referral and testing bias. As a consequence, health care professionals should be careful not to imply that there are differences in cancer risk between women who inherit a mutation from their father compared with those who inherit one from their mother.

When we see the effect of sound data analysis through correction for underlying biases by family and personal ascertainment, there appear to be two factors that may cause this spurious parent-of-origin effect. First, there seems to be a predominance of referrals of families with (multiple) affected females. Through the paternal lineage, this situation may be less likely to be present, or information on family history may be less clearly available. Second, there appears to be a genetic testing bias, which favors testing of women who have already developed cancer above testing of their unaffected relatives.

These factors demand our attention because prevention of cancer and/or mortality requires the timely referral of women at increased risk. It has been shown that the recording and interpretation of family history on the paternal side is sometimes neglected (3). Moreover, the proband's way of telling their family members about genetic test results is often weak and insufficient to convey the seriousness of the message accurately, especially when it concerns male relatives in *BRCA* families (4). The current trend of extending DNA testing criteria, such as referral of all epithelial ovarian cancer cases (5), may help to reduce referral bias. Moreover, our findings underline the need for continual education of health care workers and of the general public, as well as the need for a more proactive approach by health care professionals in informing relatives at risk, to help mitigate this problem.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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